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(54) ISOTOPICALLY LABELLED FATTY ACIDS

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TITLE OF THE INVENTION

Isotopically Labelled Fatty Acids

ABSTRACT OF THE DISCLOSURE

The present invention relates to a process for the preparation of specifically labelled fatty acids and particularly to certain tetradeuterated or trideuterated palmitic acids. The novel compounds of the present invention--specifically labelled palmitic acids including palmitic-5,5,6,6-d_4 acid, palmitic-7,7,8,8-d_4 acid, palmitic-16,16,16-d_3 acid, and palmitic-11,11,12,12-d_4 acid--are prepared by a synthetic scheme which involves a combination of steps, including the alkylation of an intermediate containing a terminal acetylenic moiety and subsequently hydrogenating or deuterogenating the acetylenic bond in the presence of the soluble hydrogenation catalyst, tris-(triphenylphosphoro)rhodium chloride, to produce the corresponding saturated compound in which the acetylenic bond is saturated with either hydrogen or deuterium. Subsequent synthetic steps are utilized to convert functional substituents by known reaction steps to a carboxylic acid substituent, thus producing the novel compounds of the present invention.

SUMMARY OF THE INVENTION

This invention relates to a process for the preparation of specifically labelled, saturated fatty acids and to the process for the preparation of specifically labelled unsaturated acids. More specifically, it relates

to multi-step syntheses of fatty acids in which the synthesis is designed to minimize the possibility of isotope scrambling. The invention further relates to the novel specifically labelled fatty acids prepared in accordance with the novel processes. Still more specifically, it relates to a group of novel specifically deuterated palmitic acids. It also relates to a novel method for producing such compounds by a synthesis which includes the steps of (1) alkylating a compound having a terminal acetylenic moiety and a terminal functional substituent convertible to carboxyl, and (2) catalytically deuterogenating the triple bond of the formed acetylenic compound, thus producing an intermediate having only one carbon-carbon linkage completely deuterated and having substantially no deuterium substitution elsewhere in the molecule.

BACKGROUND OF THE INVENTION

The processes for producing labelled fatty acids employed in the prior art involve the conversion of ordinary fatty acids to their deuterated counterparts by hydrogen-deuterium exchange under conditions leading to partial and/or complete replacement of hydrogen with deuterium in a statistical basis. This type of deuterium-hydrogen exchange is difficult to control, and impossible to limit to the preparation of specifically labelled fatty acids. Other methods involve the preparation of mixtures of partially deuterated fatty acids and the attempted separation of such mixtures into their component individual compounds by complicated isolation procedures involving gas-liquid chromatography and the like. Still other

procedures include the synthesis of unsaturated fatty acids and the catalytic deuteration of such unsaturated acids to produce the corresponding dideuterosubstituted saturated fatty acids having deuterium present in at least one specific location in the molecule. A drawback to this procedure is the tendency to cause isotope scrambling during the catalytic deuteration of such compounds. Thus, in the course of the catalytic deuteration of such compounds, one obtains, in addition to the product resulting from saturation of the double bond, a proportion of product in which other hydrogens of the substrate compound have randomly been exchanged with deuterium. This results in the preparation of a mixture of deuterated analogs, which either contaminate the specifically labelled product or which must be separated by difficult purification processes such as are mentioned hereinabove.

DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a process for the preparation of specifically labelled fatty acids using a synthetic sequence which combines the steps of alkylation of a terminal acetylenic substituent and hydrogenating or deuterogenating the acetylenic bond in the presence of a selective and soluble hydrogenation catalyst. The selection of the substrate compounds for the alkylation reaction is based on the desired position of deuterium in the final specifically labelled acid. This alkylation reaction establishes the position of the deuterium labelling relative to the carboxylic acid function in the final compound.

The process of the present invention is especially useful for the preparation of specifically labelled palmitic acids, which contain deuterium substituents specifically affixed to certain positions of the carbon skeleton. Thus, by judicious selection of the reacting species, there are prepared in accordance with the present invention, palmitic-5,5,6,6-d_4 acid, palmitic-7,7,8,8-d_4 acid, palmitic -16,16,16-d_3 acid, and palmitic-11,11,12,12-d_4 acid. The process of the present invention may also be utilized in the preparation of other specifically deuterated d_4 fatty acids, especially d_4 palmitic acids.

In accordance with the present invention, the starting materials employed include one compound containing a terminal acetylenic moiety and a second compound containing a terminal halogen substituent. The halo compound is the alkylating species, and the number of carbons in the halohydrocarbon determines the length of the alkyl substituent attached to the terminal acetylene group and therefore the ultimate specific position of deuterium atoms in the final acid. The starting material which contains the terminal acetylene moiety also contains a carboxylic acid function or another functional substituent readily convertible to carboxyl but unreactive under the conditions of the alkylation reaction. One such substituent is an hydroxyl substituent protected from reaction by derivatization as a tetrahydropyranyl ether. Following the alkylation, the tetrahydropyranyl ether is readily cleaved to produce the corresponding hydroxy compound which is carefully oxidized to the corresponding carboxylic acid compound in two stages using pyridium chlorochromate.

In another procedure, the hydroxyl substituent is first converted to a bromo substituent by treatment with a brominating agent such as carbon tetrabromide in the presence of triphenylphosphine, which in turn is metathesized with an alkali metal cyanide, e.g., potassium, to the corresponding nitrile. The nitrile compound is then converted to the corresponding carboxylic acid by hydrolysis with aqueous alkali, as for example, an alkali metal hydroxide (sodium or potassium hydroxide 20% solution in water w/v).

In one specific embodiment of the invention, the tetrahydropyranyl ether of 5-hexyn-1-ol is alkylated by treatment with 1-bromodecane in the presence of a strong base such as butylithium to produce the intermediate 5-hexadecyl-1-ol. This acetylenic alcohol is then reduced using deuterium gas in the presence of tris-(triphenylphosphoro)rhodium chloride as a catalyst to produce the corresponding saturated hexadecane-5,5,6,6-d_4-1-ol OD. The resulting saturated alcohol is then oxidized in two stages using pyridinium chlorochromate to produce the desired specifically labelled palmitic-5,5,6,6-d_4 acid.

In a second specific embodiment of the invention, the desired acid is produced directly in a two-step sequence which comprises first contacting 1-decyne with 6-bromo-hexanoic acid in the presence of butyl lithium to produce directly the acetylenic acid, 7-hexadecynoic acid, which is then converted directly to palmitic 7,7,8,8-d_4 carboxylic acid by treatment with deuterium gas and tris-(triphenylphosphoro)rhodium chloride as a catalyst.

In a further specific embodiment of the present invention, palmitic-16,16,16-d_3 acid is prepared by first contacting 10-undecyn-1-ol tetrahydropyranyl ether with 1-bromopentane-5,5,5-d_3 in the presence of butyl lithium to produce as a first intermediate, 10-hexadecyn-16,16,16-d_3-ol and subsequently hydrogenating said decynol in the presence of tris-(triphenylphosphoro)rhodium chloride to produce the desired product.

In a still further specific embodiment of the present invention, 10-undecyl-1-ol tetrahydropyranyl ether is alkylated using 1-bromobutane in the presence of butyl lithium to produce 10-pentadecyn-ol, which is converted to the tetradeutero compound pentadecan-1-ol 10,10,11,11-d_4 by treatment with deuterium gas in the presence of tris-(triphenylphosphoro)rhodium chloride as a catalyst. The said pentadecanol is then successively converted to the corresponding halo compound, 1-bromopentadecane-10,10,11,11-d_4 by treatment with triphenylphosphine and carbon tetrabromide, followed by metatheses of the bromopentadecane with potassium cyanide to produce hexadecanitrile 11,11,12,12-d_4 which in turn is hydrolyzed using 20% aqueous alcoholic sodium hydroxide solution to produce the desired palmitic-11,11,12,12-d_4 acid.

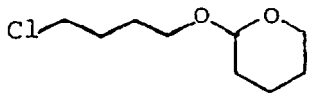
The novel, specifically labelled fatty acids of the present invention are valuable compounds used in many kinds of specialized research work in addition to their utility for the same purposes as the commercially available palmitic acid. General applications include their use in the study of reaction mechanisms, as tracers in the study of separation processes, and as model compounds for investigation of the physical properties of labelled compounds.

They are also useful in the study of the naturally occurring unlabelled acids in biological systems, and as such may be employed in the clinical diagnosis of conditions which involve the production or abstraction of fatty acids. They are also useful in the study of the metabolism and biosynthesis of the corresponding unlabelled compounds.

EXAMPLE 1

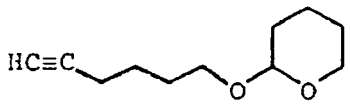
Palmitic 5,5,6,6-d_4 Acid

Step A: 4-Chlorobutanol tetrahydropyranyl ether



A mixture of 4-chlorobutanol (21.7 g.) and p-toluenesulfonic acid (250 mg.) in anhydrous ether is added to dihydropyran (26 ml.) and the reaction mixture is stirred at room temperature overnight. There is an initial mild exothermic reaction. The solution is then diluted with ether (200 ml.) and washed twice with 0.1 M sodium carbonate solution, the ether layer containing the product is dried with potassium carbonate and evaporated under reduced pressure, leaving a residue containing 4-chlorobutanol tetrahydropyranyl ether. The residue is distilled, and the fraction at 74-76°C./0.3 mm. Hg. is collected. Analytical data, n.m.r., m, 1.27-2.0, 8H; m, 3.22-4.12, 6H; s, 4.58, 1H.

Step B: 5-hexyn-1-ol-tetrahydropyranyl ether



Under a nitrogen atmosphere, and with stirring, acetylene is introduced into dry tetrahydrofuran (150 ml.), cooled, and maintained below 10°C., while butyl lithium (150 ml. of a 2.4 M solution in hexane) is added dropwise. After addition is complete, the mixture is matured for one hour. A passage of acetylene gas through the mixture is steadily maintained. A solution of 4-chlorobutanol tetra-

hydropyranyl ether (50 g.) in dry hexamethyl phosphoric triamide (250 ml.) is added dropwise at such a rate that the temperature did not exceed 20°C. The reaction mixture is stirred overnight at room temperature; ice, then water, is added to dilute the mixture to one litre, and the mixture is extracted twice with ether. The ether solution is backwashed with water, dried with potassium carbonate, and evaporated under reduced pressure to produce a residue containing 5-hexyn-1-ol-tetrahydropyranyl ether. The residue is distilled, collecting the fraction at 66-69°C. (0.25 mm. Hg.), containing principally 5-hexyn-1-ol-tetrahydropyranyl ether, b.p. 67-68°C./0.25 mm. Hg. Gas chromatographic analysis demonstrates that the product contains 5% unreacted starting material--4-chlorobutanol tetrahydropyranyl ether.

Step C: 5-Hexadecynyl-1-ol

$$CH_3(CH_2)_9C{\equiv}C(CH_2)_4OH$$

Under a nitrogen atmosphere, and with stirring and cooling, butyl lithium (66 ml. of a 2.4 M solution in hexane) is added to a solution of 5-hexyl-1-ol-tetrahydropyranyl ether (30 g.) in dry tetrahydrofuran (100 ml.), at such a rate that the temperature remains below 10°C. The reaction mixture is stirred at 10°C. for one hour, then 1-bromodecane (36.3 g.) in dry hexamethyl phosphonic triamide (120 ml.) was added at a rate such that the temperature is maintained below 25°C. The reaction is stirred at room temperature overnight under an atmosphere of nitrogen, then worked up by the addition of ice, then water, to dilute the reaction to 700 ml., and is extracted twice with ether. The combined ether extracts are washed several times with water, dried over potassium carbonate, and

evaporated at reduced pressure. The residue is warmed at 50°C. for two hours in methanol (200 ml.) containing p-toluenesulfonic acid (250 mg). The methanolic solution is reduced to a quarter its volume, 0.1 M sodium carbonate solution (100 ml.) is added, and the mixture is extracted with ether. The ether extract containing the product is backwashed with 0.1 M sodium carbonate solution, then with water, dried over magnesium sulfate, and evaporated under reduced pressure. The low boiling material is mainly removed by distillation at 0.1 mm. ($<$ 80°C.), and the residue is chromatographed on silica gel, eluting with hexane, then hexane containing 3% ethyl acetate, containing 10% ethyl acetate and finally 20% ethyl acetate. The purified product, 5-hexadecyl-1-ol, is characterized by n.m.r., $CDCl_3$ TMS, t, 3H, 0.88 ppm; m, 1.27, 16H; m, 1.6, 4H; m, 2.15, 4H; t, 3.63, 2H.

Step D: Hexadecane-5,5,6,6-d_4-1-ol

$$CH_3(CH_2)_9CD_2(CH_2)_4OH$$

The hydroxyl group of 5-hexadecyl-1-ol is exchanged by washing an ethereal solution of the compound several times with excess deuterium oxide. The recovered 5-hexadecyn-1-ol-OD (16 g.) is dissolved in 500 ml. of dry, oxygen-free toluene; and under an atmosphere of nitrogen, tris-(triphenylphosphoro)rhodium chloride (0.5 g.) is added as a catalyst. The acetylenic compound is reduced with D_2 gas at 1 atmosphere pressure, taking up the calculated volume of deuterium. The toluene solution is evaporated under reduced pressure; the residue is extracted with ether

several times; and combined extracts are filtered and evaporated to dryness. The residue is distilled 125-128°C. (0.2 mm. Hg.), giving 14 g. of product.

Step E: Hexadecanal-5,5,6,6-d_4

$$CH_3(CH_2)_9CD_2CD_2(CH_2)_3CHO$$

In an appropriate flask fitted with a reflux condensor is suspended 8.4 g. (86 mmole) of pyridinium chlorochromate prepared as described in E. J. Corey and J. William Suggs Tetrahedron Letters, p. 2647 (1975), in 100 ml. anhydrous methylene chloride. A solution of hexadecane-5,5,6,6-d_4-1-ol (14 g., 57 mmole) in 20 ml. methylene chloride is added in one portion to the stirred solution. After 1.5 hours, 100 ml. of dry ether is added and the supernatant decanted from the black gum, which separates from the reaction mixture. The insoluble residue is then washed thoroughly three times with 50 ml. portions of anhydrous ether; whereupon the insoluble black gum residue becomes a black granular solid. The decanted supernatant solution is combined with the ether extracts containing the product and passed through a filter pad; and the solvent is removed by distillation under reduced pressure, leaving the product as a residual oil. The product is purified by distillation at 115-120°C. (0.15 mm.), thereby providing substantially pure hexadecanal-5,5,6,6-d_4, b.p. 115-120°C./0.15 mm. Hg. The undistilled residue comprising principally palmitoyl 5,5,6,6-d_4-palmitate 5,5,6,6-d_4 is recycled by reduction of the ester with lithium aluminum hydride in ether to the starting material, hexadecanol-5,5,6,6-d_4.

Step F: Palmitic-5,5,6,6-d_4 Acid

$$CH_3(CH_2)_9CD_2CD_2(CH_2)_3COOH$$

To a stirred, cooled suspension of hexadecanal 5,5,6,6-d_4 (7.5 g.) in 100 ml. of acetic acid is added, dropwise, chromic acid (4.7 g.) in water (10 ml.) over a period of 45 minutes. The temperature is maintained below 55°C. The reaction is stirred for a further hour, diluted with H_2O to 500 ml., and extracted with ether (3 X 150 ml.). The combined ether extracts are washed with H_2O (5 X 200 ml.), dried over magnesium sulfate, and evaporated. Residual acetic acid is removed by distillation with toluene. The crude acid is purified by distillation 154-157°C. (0.15 mm.) and crystallization from petroleum ether (30-60°C.) at low temperature to afford substantially pure palmitic-5,5,6,6-d_4 acid, m.p. 63°C (lit 63°C. of the corresponding light palmitic acid). Mass spectrum M^+ = 260 (d_4) = 96.95%, 259 (d_3) = 3.05%; (98.98 atom %).

EXAMPLE 2

Palmitic 7,7,8,8-d_4 Acid

Step A: 7-Hexadecynoic Acid

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_5COOH$$

A solution of 1-decyne (14 g.) in dry tetrahydrofuran (40 ml.) is cooled in an atmosphere of nitrogen to <0°C. Butyllithium (45 ml. of 2.4 M solution) in hexane is added at such a rate that the internal reaction temperature does not exceed 10°C. When addition is complete, the

solution of 1-lithiodecyne is matured for one hour at 5-10°C.; and the 6-bromo-hexanoic acid in 40 ml. of dry hexamethyl phosphonic triamide is added at a rate such that the reaction does not go above 25°C. After addition is complete, the reaction is stirred at room temperature overnight. The reaction mixture is diluted with ice and water, acidified to pH 2, and extracted with ether. The combined ether extracts are backwashed with H_2O, dried over magnesium sulfate, and evaporated under reduced pressure. The residue containing the product is distilled. The first fraction is reasonably pure, unreacted 1-decyne (~8 g.), then the temperature rises over a few minutes to 155°C. at 0.1 mm. The product is then recovered substantially pure as an oil.

Step B: Palmitic-7,7,8,8-d_4 Acid

$$CH_3(CH_2)_7CD_2CD_2(CH_2)_5COOH$$

The 7-hexadecynoic acid is converted to the methyl ester with methanol and hydrogen chloride. The ester is reduced in a manner analogous to the reduction of 5-hexadecyn-ol as described in Example 1, Step D. The recovered methyl palmitate 7,7,8,8-d_4 is converted to the acid by hydrolysis with sodium hydroxide in aqueous methanol. The acid is crystallized from petroleum ether at low temperature; m.p. 63-63°C.

EXAMPLE 3

Palmitic 16,16,16-d_3 Acid

Step A: 10-Undecyn-1-ol tetrahydropyranyl ether

$$HC{\equiv}C(CH_2)_9OTHP$$

10-undecynoic acid is reduced with lithium

aluminum hydride in ether, by standard procedures, to the 10-undecyn-1-ol. The 10-undecyn-1-ol is converted to its tetrahydropyranyl ether by a method analogous to that described above from 4-chlorobutanol (Example 1, Step A).

Step B: 1-bromopentane 5,5,5-d_3

$$CD_3(CH_2)_4Br$$

Ethyl-2,2,2-d_3 bromide (45 g.) is added dropwise to a cooled, stirred suspension of Mg. (9.35 g.) in 200 ml. of anhydrous ether. After the Grignard reagent has formed, trimethylene oxide (27 g.) in anhydrous ether (60 ml.) is added over 2-3 minutes. The reaction mixture is refluxed for one hour, then dry benzene is added slowly while the ether is distilled out. After all ether has been replaced with benzene, the reaction is refluxed for a further 3 hours. Saturated ammonium chloride solution is then added slowly to the cooled reaction mixture. The mixture, after acidification with hydrochloric acid solution, is extracted with ether (4 X 100 ml.); the combined extracts are dried over magnesium sulfate and evaporated under reduced pressure until most of the ether is removed. The residue is distilled through a Vigreux column, and two major fractions are collected. The first at ~60°C., the second at 134-140°C. The second fraction is crude 1-pentanol (14 g.).

A mixture of the above product, triphenylphosphene (45.2 g.), and dimethylformamide is treated with bromine until the orange colour persists. The reaction is stirred for a further hour, and the volatile material, including dimethyl formamide, is removed under reduced

pressure. To the distillate is added H_2O (600 ml.). The lower layer is carefully separated, backwashed twice with water, dried over magnesium sulfate, and filtered. The magnesium sulfate is extracted twice with ether, and the combined washings and product layer are combined and distilled. Pure 1-bromopentane 5,5,5-d_3 is obtained. Single peak by g.c.

Step C: 10-Hexadecyn-16,16,16-$d_3$ol

$$CD_3(CH_2)_4C{\equiv}C(CH_2)_9\text{-}OH$$

Using 10-undecyn-1-ol tetrahydropyranyl ether (34.5 g.) and 1-bromopentane 5,5,5-d_3 (35 g.), 10-hexadecyn-1-ol-16,16,16-d_3 is prepared in a manner analogous to that described for 5-hexadecyn-1-ol (Example 1, Step C). The product is partially separated from the major impurity 10-undecyn-1-ol by column chromatography and used in the next step without further purification.

Step D: Hexadecan-1-ol 16,16,16-d_3

$$CD_3(CH_2)_{14}CH_2OH$$

The crude 10-hexadecyn-1-ol 16,16,16-d_3 obtained above is reduced with H_2 in the presence of tris-(triphenylphosphoro)-rhodium chloride as described for 5-hexadecyn-1-ol. The crude recovered product is carefully distilled, giving pure hexadecan-1-ol 16,16,16-d_3; b.p. 115-118°C./0.15 mm. Hg.

Step E: Palmitic 16,16,16-d_3 Acid

$CD_3(CH_2)_{14}COOH$

The hexadecan-1-ol 16,16,16-d_3 is oxidized in two steps using pyridinium chlorochromate then chromic acid in acetic acid as described for hexadecan-1-ol 5,5,6,6-d_4 (Example 1, Steps E and F), to give, after the same purification procedure, palmitic 16,16,16-d_3 acid; m.p., 63°C.

EXAMPLE 4

Palmitic 11,11,12,12-d_4 Acid

Step A: Pentadecan-1-ol 10,10,11,11-d_4

$CH_3(CH_2)_3CD_2CD_2(CH_2)_9$-OH

Pentadecan-1-ol 10,10,11,11-d_4 is prepared in an exactly analogous manner to hexadecan-1-ol 16,16,16-d_3 (described in Example 3), except 1-bromobutane is used in place of 1-bromopentane 5,5,5-d_3 and deuterium is used in place of hydrogen in the reduction step.

Step B: 1-Bromopentadecane 10,10,11,11-d_4

$CH_3(CH_2)_3CD_2CD_2(CH_2)_9Br$

Triphenylphosphine (11.3 g.) is added to a mixture of ether (80 ml.), carbon tetrabromide (14.3 g.), and pentadecan-1-ol 10,10,11,11-d_4; and the reaction mixture is then refluxed. The progress of the reaction is monitored by gas chromatographic analysis of aliquots taken from the reaction mixture. After five hours, the reaction

is complete. Solvent is removed under reduced pressure, and the residue filtered through a column of silica gel, eluting with hexane. The product is collected and distilled to give substantially pure 1-bromopentadecane 10,10,11,11-d_4 (~130°C./0.2 mm. Hg.).

Step C: Hexadecanitrile 11,11,12,12-d_4

$$CH_3(CH_2)_3CD_2CD_2(CH_2)_9CN$$

A mixture of 1-bromopentadecane 10,10,11,11-d_4 (5.9 g.), potassium cyanide (2.6 g.), and ethanol (60 ml.) are refluxed. The reaction is monitored by t.l.c. (thin layer chromatography). After refluxing overnight, the reaction is complete. The reaction is cooled, evaporated to a small volume, diluted with ether, and washed with 0.1 M sodium hydrogen carbonate solution, and extracted with ether. The ether solution is dried and evaporated, leaving hexadecanitrile 11,11,12,12-d_4 as a product, which is identified by n.m.r. $CDCl_3$, t, 3H, 0.88; m, 1.28, 22H; t, 2H, 2.30, and i.r. [C-D, 2090 cm^{-1}, 2190 cm^{-1}].

Step D: Palmitic-11,11,12,12-d_4 Acid

$$CH_3(CH_2)_3CD_2CD_2(CH_2)_9COOH$$

Hexadecanitrile 11,11,12,12-d_4 (4.8 g.) is combined with 20% sodium hydroxide solution (20 ml.) and ethanol (100 ml.) and refluxed for 16 hours. All nitrile is consumed by the procedure as demonstrated by t.l.c. The mixture is carefully acidified with aqueous hydrochloric acid. The ethanol is largely removed by evaporation at reduced pressure, and the mixture is extracted with ether.

The ether solution is washed once with water, dried over magnesium sulfate, and evaporated. The acid product is crystallized at low temperature from petroleum ether (30-60°C.), m.p. 62-63°C.

WHAT IS CLAIMED IS:

1. A process for the preparation of specifically labelled fatty acids which comprises the steps of alkylating a terminal acetylene substituent in an aliphatic compound having a carboxyl substituent or a functional substituent convertible to carboxyl and subsequently hydrogenating or deuterogenating said acetylenic substituent to produce a specifically labelled fatty acid or compound readily convertible thereto.

2. A process according to Claim 1 which comprises conducting the hydrogenation or deuterogenation reaction in the presence of a catalyst which is soluble in the reaction mixture.

3. A process according to Claim 2 wherein the catalyst is tris-(triphenylphosphoro)rhodium chloride.

4. A process according to Claim 1 which comprises the steps of alkylating a terminal acetylene substituent in an alkynoic acid and subsequently deuterogenating said acetylenic substituent to produce a tetradeuterated aliphatic carboxylic acid.

5. A process according to Claim 1 which comprises the steps of alkylating the terminal acetylene substituent in an alkyn-1-ol, subsequently deuterogenating said alkylated alkyn-1-ol, to produce the corresponding tetradeuterated alkan-1-ol and converting said alkanol by known means to the corresponding tetradeuterated aliphatic carboxylic acid.

6. A process according to Claim 1 which comprises the steps of alkylating a terminal acetylene substituent in an alkyn-1-ol by treatment with a deuteroalkyl halide in the presence of butyl lithium to produce a deuteroalkylalkyn-1-ol, subsequently hydrogenating said deuteroalkylalkyn-1-ol to produce the corresponding deuteroalkanol and converting said alkanol by known means to a specifically deuterated aliphatic carboxylic acid.

7. A process according to Claim 1 which comprises contacting 5-hexyn-1-ol tetrahydropyranyl ether with 1-bromodecane in the presence of butyl lithium to produce 5-hexadecyn-1-ol and subsequently contacting said hexadecynol with deuterium gas in the presence of tris-(triphenylphosphoro)rhodium chloride to produce hexadecane 5,5,6,6-d_4-1-ol and subsequently converting said hexadecanol by known means to palmitic-5,5,6,6-d_4 acid.

8. A process according to Claim 1 which comprises contacting 1-decyne with 6-bromohexanoic acid in the presence of butyl lithium to produce 7-hexadecynoic acid and subsequently contacting said hexadecynoic acid with deuterium in the presence of tris-(triphenylphosphoro)rhodium chloride to produce palmitic-7,7,8,8-d_4 acid.

9. A process according to Claim 1 which comprises contacting 10-undecynol tetrahydropyranyl ether with 1-bromopentane-5,5,5-d_3 in the presence of butyl lithium to produce 10-hexadecyn-1-ol 16,16,16-d_3 and subsequently

contacting said hexadecynol with hydrogen in the presence of tris-(triphenylphosphoro)rhodium chloride to produce hexadecan-1-ol-16,16,16-d_3 and converting said hexadecanol by known means to palmitic-16,16,16-d_3 acid.

10. A process according to Claim 1 which comprises contacting 10-undecyn-1-ol with 1-bromobutane in the presence of butyl lithium to produce 10-pentadecyn-1-ol and subsequently contacting said pentadecyn-1-ol with deuterium gas in the presence of tris-(triphenylphosphoro)-rhodium chloride to produce pentadecan-1-ol 10,10,11,11-d_4, converting said pentadecanol by bromination to the corresponding 1-bromopentadecane 10,10,11,11-d_4, contacting said bromopentadecane with potassium cyanide to produce hexadecanitrile 11,11,12,12-d_4, and hydrolyzing said nitrile to produce palmitic-11,11,12,12-d_4 acid.

11. A specifically deuterated fatty acid compound selected from palmitic 5,5,6,6-d_4 acid, palmitic 7,7,8,8-d_4 acid, palmitic 16,16,16-d_3 acid, and palmitic 11,11,12,12-d_4 acid.

12. Palmitic 5,5,6,6-d_4 acid.

13. Palmitic 7,7,8,8-d_4 acid.

14. Palmitic 16,16,16-d_3 acid.

15. Palmitic 11,11,12,12-d_4 acid.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente